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Lessons for cannabinoid regulation from electronic nicotine delivery system product regulation

Brian Yagi[1], Stan Veuger[2], Brian J. Miller[2,3], Paul Larkin[4,*]

[1]Division of Hospital Medicine, Department of Medicine, University of Michigan Medical School, Ann Arbor, MI 48109, United States
[2]Division of Hospital Medicine, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD 21287, United States
[3]American Enterprise Institute, Washington, DC 20036, United States
[4]The Heritage Foundation, Washington, DC 20002, United States

*Corresponding author: The Heritage Foundation, Washington, DC 20002, United States. Email: Paul.LarkinJr@heritage.org

Abstract

Cannabis legalization continues to spread, with 38 states permitting the use of medical marijuana, 22 states permitting recreational use, and growing political momentum for federal legalization. The last time the Food and Drug Administration (FDA) was tasked with regulating a new product occurred with 2009's Family Smoking Prevention and Tobacco Control Act, which created the Center for Tobacco Products (CTP). Thus, the time is ripe to review the history of CTP with particular attention to difficulties the nascent center faced in regulating novel products such as e-cigarettes or electronic nicotine delivery systems (ENDS). Specifically, FDA has struggled with defining its scope of authority, determining which review pathway(s) to utilize, and promulgating timely and transparent product standards for marketing authorization—all of which offer lessons for improving cannabis product oversight and enforcement.

Key words: FDA policy; tobacco regulation; ENDS product regulation; Center for Tobacco Products; cannabis regulation.

Introduction

Cannabis consumption continues to grow, with over 50 million US adults spending $95.1 billion on medical and recreational products in 2024.[1,2] Products available for purchase come in a variety of forms including the *Cannabis sativa* plant, which are consumed via combustion and inhalation, or extracts/infusions consumed as vaporized aerosols, edibles, potables, or topicals. Thousands of unique products have wide ranges of tetrahydrocannabinol (THC) concentration,[3] with product diversity increasing rapidly.[4] Given the interplay between federal laws that prohibit cannabis and the multitude of state laws that permit its cultivation, possession, sale, and use,[5] product regulation is currently left to each state, with significant differences in scope.[6,7] Efforts to legalize cannabis on the federal level have included proposed legislation[8] and the Executive Branch's recommendation to re-schedule cannabis from Schedule I to Schedule III.[9,10] In this changing environment, recent efforts to promote oversight of addictive products, such as the 2009 creation of the US Food and Drug Administration's (FDA's) Center for Tobacco Products (CTP), offer pragmatic lessons in regulatory policy. Under the current statutory structure created through the 2009 Family Smoking Prevention and Tobacco Control Act (TCA), tobacco products are largely regulated by a separate center within FDA (CTP), while nicotine-replacement products making therapeutic claims are regulated by the Center for Drug Evaluation and Research (CDER). In contrast, cannabis-derived products are regulated under FDA's general authorities for drugs, dietary supplements, and foods, which the FDA claims are inadequate.[11]

The recent history of tobacco products demonstrates how the FDA continues to struggle in executing its statutory mission, especially in its regulation of electronic nicotine delivery systems (ENDS), the newest and most rapidly changing formulation of tobacco products. A recent third-party review by the Reagan-Udall Foundation was critical of FDA for its lack of transparency—finding that application requirements are "vague and frequently changing" and that the center's decisions to authorize or deny a product lack "clarity, transparency, and communication"—and recommended that FDA pivot from a reactive mode to a proactive mode in order to focus on its primary mission as a product regulator.[12] This article, representing a contrasting perspective to current, recent FDA assertions that it lacks authority, examines recent challenges in tobacco product regulation and delineates 3 key lessons learned from the first 14 years of FDA tobacco regulation to inform potential future oversight of cannabis.[13] Specifically, we denote the FDA's failure to exercise its existing authorities to take enforcement action against a litany of currently illegally marketed cannabis products making unauthorized therapeutic claims, outdated guidance that fails to ensure that botanical products meet FDA standards, and other core agency regulatory failures.

Lesson 1: Failing to clearly define FDA's scope and authority leads to regulatory delays

Congress passed the TCA in 2009, bringing tobacco products under FDA jurisdiction. The TCA enumerated 6 specific

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product classes subject to FDA regulation but did not specifically list ENDS.[14] The FDA issued a formal notice-and-comment rule deeming ENDS to be included as a "tobacco product,"[15] securing its authority to regulate ENDS in December 2019[16] after the resolution of multiple legal challenges. Subsequent controversy arose over FDA's regulatory authority over synthetic nicotine products created in laboratories,[17] a loophole that Congress corrected in March 2022, amending the definition of tobacco product to include "any product made or derived from tobacco, or containing nicotine from any source, that is intended for human consumption."[18] Notably, this definition also encompasses ENDS, meaning that, if Congress had originally enacted oversight with this statutory language, it would have avoided oversight fragmentation.

Early attempts to oversee cannabis markets have faced similar problems with statutory definitions of the regulated product resulting in regulatory fragmentation. Currently, the dominant federal statute on cannabis is the Controlled Substances Act of 1970 (CSA), which placed cannabis in Schedule I (the most restrictive) and authorized the Drug Enforcement Administration (DEA) to restrict its possession, use, sale, manufacture, and importation.[13,19]

Subsequently, the 2018 Farm Bill carved out hemp from the CSA definition as any cannabis plant containing less than 0.3% THC based on the premise that it is non-psychoactive[20] and placed hemp under the regulatory control of the US Department of Agriculture (USDA).[21] That legislation effectively created a legal market nationwide for hemp-derived, cannabidiol (CBD)-only products marketed as non-prescription products containing other cannabinoids (with <0.3% THC), even in states that have not legalized medical or recreational cannabis products.

The FDA currently retains authority over supplements, including cannabinoids with more than 0.3% THC. These products do not meet the standard for marketing as a supplement as these cannabinoids are currently available as pharmaceutical-grade, prescription THC and CBD products requiring a physician's order and supervision. The statutory standard for supplement marketing is "generally recognized as safe" and excludes compounds currently marketed as drugs. That is, products cannot be simultaneously marketed as a prescription drug and as a supplement. Instead of enforcing the law as written, in this setting the FDA has declined to exercise regulatory authority over this marketplace through vigorous enforcement, claiming that it lacks authority to regulate CBD products as a supplement[22]—an agency policy choice in contravention of the law.

Thus, the FDA should undertake additional review and broader, frequent, and more sustained enforcement action against a wider range of illegally marketed supplement products. Any future statutory updates to the Farm Bill or other legislation affecting cannabinoid product regulation should aim to provide clarity regarding regulatory jurisdiction and scope, with a carefully sculpted statutory definition to ensure that the desired agency or agencies has oversight and enforcement authority over the wide variety of cannabinoid products (cannabis; extracts including vaporized products; concentrate/infusible products, eg, edibles, topicals; and synthetic cannabinoids such as delta-8).

Lesson 2: Provide oversight through appropriate centers and review pathways

The FDA's CDER is responsible for regulating pharmaceutical products that make therapeutic claims on their labels, including those that treat tobacco use disorder: pharmacotherapy and nicotine replacement therapy (NRT). Applicants must submit a New Drug Application (NDA), which is reviewed for safety and effectiveness for the proposed medical indication (eg, reducing nicotine cravings), which typically requires "two adequate and well-controlled" supporting clinical trials.[23] By contrast, CTP reviews ENDS for premarket authorization based on whether the product is deemed "Appropriate for the Protection of the Public Health" (APPH), a novel epidemiologic regulatory standard. The FDA has left the decision to product manufacturers on which pathway to apply based on the products' intended label and claims.[24]

The FDA's approach to tobacco products, however, has had several problems: as of January 2024, FDA has not approved any ENDS as a cessation tool, despite a growing body of evidence that ENDS are more effective at smoking cessation than traditional NRT products in at least some circumstances.[25,26] Unfortunately, both physicians and patients are misinformed about the risks and potential benefits of ENDS, mistaking them for being equally harmful as combustible products.[27,28] This has delayed the public health goal of harm reduction,[29,30] with models estimating that approximately 1.8 million lives could be saved by 2060 if ENDS are substituted for combustible products.[31]

Currently, the FDA regulates cannabis-derived products under its general authorities for different product classes, such as drugs, dietary supplements, or foods, and has published several public resources on how it applies those authorities for cannabis-derived products.[11] For example, if the producer of a cannabis-derived product wishes to label or market the product with therapeutic claims, it is regulated as a pharmaceutical product. This is also how FDA distinguishes ENDS from NRT used to treat tobacco use disorder, requiring approval through CDER. It also mimics how the FDA distinguishes a pharmaceutical product from a dietary supplement. For example, if a product claims an effect on the structure or function of the body but does not make any therapeutic or health claims, it is categorized as a dietary supplement (with the agency noting that it lacks the authority to use this framework to oversee CBD products).[22] The FDA's Center for Food Safety and Applied Nutrition (CFSAN) regulates dietary supplements, which are subject to significantly less onerous evidentiary requirements for marketing authorization and post-market safety surveillance.[32]

Recent FDA actions demonstrate how the agency has attempted to learn from its mistakes in tobacco regulation. The CDER has approved several pharmaceutical-grade, purified cannabinoids for use as a prescription drug under the supervision of a physician for specific medical indications based upon evidence from clinical trials submitted as part of an NDA. In 2018, CDER approved GW Research Ltd.'s cannabidiol (Epidiolex), which contains a chemically purified form of CBD, for treatment of 2 forms of pediatric epilepsy. The CDER has also approved dronabinol and nabilone, synthetic forms of delta-9 THC,[33] for the treatment of chemotherapy-associated nausea and AIDS-associated

anorexia. Of note, all 4 medications are chemically purified, pharmaceutical-grade compounds of a manufactured nature that follows that of traditional pharmaceutical products rather than the botanical form or infusion products available at commercial dispensaries.

In contrast to laboratory-synthesized cannabinoids, cannabis in its plant form is difficult to regulate as a drug through CDER.[34-36] While there is emerging low-quality evidence that cannabinoids may be effective for insomnia,[37] post-traumatic stress disorder (PTSD),[38] chronic pain,[39-41] and anxiety,[42] the evidence has not risen to the level of clinical significance. In the absence of meeting the standard of FDA approval as a drug, many consumers are attempting to self-treat these conditions with cannabis products available recreationally.[43] The proliferation of products that contain delta-8 THC compounds this problem. While delta-8 products are derived from plants that technically qualify as "hemp" with less than 0.3% THC, they subsequently undergo laboratory-based purification that concentrates the THC to intoxicating levels.[44] Manufacturers of these products use the loophole created by the Farm Bill to market these products, even in states that did not legalize cannabis, including through tobacco retail channels that are much more accessible to underage consumers.[45] A secret-shopper analysis of cannabis dispensaries found that numerous products contain health claims on their label, including those in recreational dispensaries (ie, pain management, anxiety, insomnia, depression, and stress).[3] The only FDA-approved therapeutic claims are for other indications and are for pharmaceutical-grade products available by prescription only, not for plant- or extract-based products available at dispensaries.[33] Thus, cannabis products are being illegally marketed without evidence supporting therapeutic claims, with dispensaries inappropriately utilizing state regulation as a rationale for bypassing FDA oversight.

Appropriate FDA oversight of products' labels and claims would assure consumers that there was biomedical evidence supporting therapeutic claims, as any cannabinoid-containing product with a therapeutic claim on its label would be required to submit safety and efficacy data to support those claims. In the context of conflicting state and federal laws and the blurring of the medical vs recreational divide, the FDA should update its nearly decade-old botanical products guidance[46] and issue guidance on clinical trial design for cannabinoid pharmaceutical product development. The FDA should continue to support deterrence enforcement by issuing timely and assertive warning letters to the many marketers of cannabis-derived products with unapproved health claims—an action that it has taken in only limited circumstances, most recently in 2021.[47] Furthermore, the FDA can coordinate with the Federal Trade Commission's Bureau of Consumer Protection Division of Marketing Practices, as appropriate, in order to ensure that the right enforcement authorities are utilized in the right circumstance.

For cannabinoid-containing products that are not intended to be marketed with therapeutic claims, some experts have proposed that an authorization pathway focused on harm reduction be enacted. While there is limited evidence demonstrating the relative risks of combustible vs vaped cannabis products, the analogous learnings from the tobacco product marketplace may apply, with combustible tobacco associated with increased risks of cardiovascular disease, chronic obstructive pulmonary disease, and a wide variety of cancers.[48] Instead of enacting science-based regulation far ahead of scientific research, policymakers should direct the National Institutes of Health (NIH) to conduct and/or fund research on the short- and long-term health effects of combustible vs vaped cannabis-derived products along with delineating and creating an evidence base around core consumer protection issues such as drug-impaired driving, the risks of secondhand smoke, and other critical science-based policy issues.

Recognizing that the state-legalized recreational market is already larger than the medical market (~65% market share projected to be ~75% by 2028),[2] when robust, high-quality scientific evidence is eventually available, federal policymakers will need to decide if it is preferable to continue using the "states as laboratories" model and to subsequently find a way to continue to build upon existing state-based oversight of recreational products or, if appropriate and if scientific evidence is supportive, to pursue, as other experts have suggested, a federal model based upon a scientific standard such as a harm-reduction standard for nonpharmaceutical cannabis akin to federal tobacco product oversight.[49]

Currently, scientific evidence does not suggest a clear path forward and, consequently, federal policymakers should focus their efforts on oversight of FDA to ensure that robust enforcement action is taken. If cannabis is rescheduled from Schedule I to III, policymakers should direct the NIH to conduct or fund research on the relative risks of cannabis products and core scientific questions around consumer protection issues. Finally, while consideration of rescheduling has historically been a purely administrative process, due to the magnitude of the scientific, clinical, policy, and political issues, these questions would benefit from robust bipartisan congressional oversight in conjunction with any potential Executive Branch action, as opposed to lone Executive Branch action.

Lesson 3: Promulgate product standards in timely fashion

The FDA has faced problems with timeliness and transparency in regulating ENDS. In May 2016, FDA determined that all ENDS, including those already on the market, needed to submit a Premarket Tobacco Product Application (PMTA) to gain market authorization. The initial deadline for submission was November 8, 2018,[50] which was subsequently pushed back to 2022.[51] The CTP received 6.5 million PMTAs for ENDS products,[52] with the accompanying delays in agency review frustrating public health and medical organizations, which sued CTP arguing that these arbitrary deadlines were an abuse of its enforcement discretion. The federal courts agreed,[53] and set a deadline for CTP's authorization or denial for September 9, 2021.[54] The CTP failed to meet that deadline for approximately 7% of applications, including then-market-share leaders JUUL and Vuse.[55] The CTP estimates that over 17 million ENDS units that had not filed a PMTA, a substantial illicit market, were available for purchase between 2021 and 2022. In March 2022, the outgoing CTP director reported that, over the preceding 12 years, CTP had conducted 1.2 million inspections, issued 105 000 warning letters, filed for 25 000 civil money penalties, and issued 220 no-tobacco-sale orders.[56] In October 2022, FDA and the Justice Department initiated the first injunction proceedings to enforce the premarket review requirement against 6 companies that failed to file a PMTA.[57]

When FDA eventually issued marketing orders and denials for ENDS PMTAs, it again frustrated the public health community with the agency's lack of transparency in how it reached its decisions. In June 2019, FDA published a guidance document regarding the information it requires in a PMTA application that lacked objective cutoffs, evidentiary standards, or references to existing scientific or private marketing standards.[58] In other words, the FDA offered no interpretation of what product performance or other forms of evidence could potentially qualify as APPH. Rather than issuing such product standards prospectively, FDA claimed that it reviewed each PMTA application individually and issued product-by-product decisions. This notion was contested when 55 000 flavored ENDS PMTAs were denied on the same day[59] and subsequent journalistic investigation revealed that CTP leadership circulated an internal memo—the "Fatal Flaw Memo"—regarding those Marketing Denial Orders (MDOs).[60] The Fatal Flaw Memo contradicted the earlier guidance document that told industry, "FDA does not expect that applicants will need to conduct long-term studies to support an application."[57] Instead, the internal agency memo instructed reviewers to deny all applications for flavored ENDS that did not contain any long-term clinical studies, such as a cohort study or a randomized controlled trial.

The CTP undertook a similar strategy when it issued MDOs for menthol-flavored ENDS in January 2023,[61] circulating an internal memo rather than public-facing product standards. This approach of using internal memoranda rather than public administrative rulemaking or issuance of guidance containing product standards is being contested in several lawsuits arguing a violation of the Administrative Procedures Act. Seven federal circuits have upheld CTP's decisions and 2 have sided against CTP's decisions, setting the stage for upcoming Supreme Court review.[62]

In hindsight, FDA's challenges regulating ENDS could have been avoided with the timely promulgation of product standards, including objective, bright-line cutoffs regarding their physical components (eg, nicotine content, vapor toxicity cutoffs); product specifications such as coil heat; and container size. The FDA has the in-house scientific testing capabilities to identify and quantify all possible chemicals in inhaled tobacco products and has issued $424 million in funding over nearly a decade to academic institutions referred to as Tobacco Centers of Regulatory Science,[63-65] with recent commentary noting that there is a sufficient quantity of unbiased scientific evidence to support ENDS product standards.[66] Furthermore, recognizing that the APPH standard is an epidemiological standard, FDA should have issued guidance as to its proposed analysis framework and evidentiary burden, so as to guide product manufacturers, internal agency review staff, and public health experts. Promulgating good guidance would have allowed FDA to enshrine the principles of harm reduction into the APPH standard and shift tobacco users to lower-risk products while simultaneously working to advance consumer protection and public health goals.

Safety signals have flared in the absence of appropriate FDA oversight within its statutory authority. In early 2019, there was an unexplained proliferation in acute lung injuries among users of e-cigarettes or vape pens, leading to the moniker "e-cigarette, or vaping, product-associated lung injury" (EVALI).[67] The majority of patients diagnosed with EVALI used products containing THC with untested and unregulated vitamin E acetate as a carrier oil, which caused acute diffuse alveolar damage or fibrinous pneumonitis.[68,69] This form of product adulteration underscores the need for proactive product oversight.

For cannabis products without therapeutic claims, safety and marketing regulation continues to be left to the states that permit its sale and use. There is tremendous heterogeneity in the thousands of cannabinoid-containing products currently available: a 2021 phytochemical analysis of cannabis strains available in several states showed significant differences between the products (as well as discrepancies between the products and their labels),[70] confirming results from a similar study performed in 2016.[71] There has been a precipitous rise in the concentrations and quantities of cannabinoids available for recreational purchase without needing to demonstrate short- or long-term product safety.[72] The proliferation of delta-8 THC products purified from hemp extracts unfolded without premarket regulatory overview for safety or Good Manufacturing Practices, allowing for adverse events due to either product adulteration or delta-8 THC itself.[73]

As seen with ENDS, even if cannabis is down-scheduled, the illicit market for cannabis products will continue to evolve.[74] In general, FDA retains the authority over products making therapeutic claims that are thus considered to be marketed as a drug under the Food, Drug, & Cosmetic Act. Therefore, the FDA will need to undertake vigorous enforcement against a litany of currently marketed products with unproven health claims and issue updated botanical products guidance and, as appropriate, product standards for pharmaceutical-grade products that have high-quality scientific evidence in the form of clinical trials that seek marketing approval as a drug.

While the FDA has yet to fully exercise its existing oversight and enforcement authority over a wide variety of cannabis products making medical claims, recreational market enforcement gaps will be filled by state authorities and, depending upon administration policy, the DEA. State regulatory authorities should also undertake the promulgation of product standards and work to remove unsafe products from the marketplace.

Conclusion

Creating a pre-market regulatory framework on top of a pre-existing post-market environment is akin building an airplane while flying it. For over a decade, FDA struggled with tobacco product oversight, with an unclear scope of authority, inappropriate delineation of regulatory boundaries, and a failure to proactively guide market participants through product standards and guidance. Navigating existing regulatory frameworks, better utilizing existing enforcement and oversight authorities, clarifying regulatory scope and jurisdiction, and ensuring the issuance of proactive regulatory guidance—coupled with pragmatic product oversight—will ensure that regulators do not repeat past mistakes as they look to improve oversight of evolving cannabis product marketplaces.

Supplementary material

Supplementary material is available at *Health Affairs Scholar* online.

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